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High bisphosphonate treatment rates and the prevalence of atypical femoral fractures in patients with systematic lupus erythematosus: a single-center retrospective study performed in Japan

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Abstract

Treatment of systemic lupus erythematosus (SLE) often continues with moderate-to-low doses of glucocorticoids for the long term. Bisphosphonates aid in the prevention and management of glucocorticoid-induced osteoporosis (GIOP). However, long-term use of bisphosphonates increases the relative risk of atypical femoral fracture (AFF) and the incidence is typically 16 or 113 per 100,000 person-years in patients treated with bisphosphonates for 5 or 10 years, respectively. Here, we explored bisphosphonate prescription rate and prevalence of AFF in patients with SLE. In total, 270 patients with SLE were enrolled. The Japanese Society for Bone and Mineral Research Guideline 2014 for GIOP management and treatment was used. We also explored AFF history through medical records. Most ($n=251$) patients were recommended to treat by the GIOP guideline (scores ≥ 3); bisphosphonates, denosumab, teriparatide, or active vitamin D was prescribed for 85.7%. Bisphosphonates were currently used by 66.1% of the patients, and 65% had used them for ≥ 5 years. Of all patients, 76.7% had a history of bisphosphonate use, 5 of 270 (1.9%) had histories of AFF. Four of five patients with AFF had taken bisphosphonates for ≥ 3.5 years, in addition to moderate doses (≥ 10 mg/day) of glucocorticoids. For the SLE patients with a history of bisphosphonate use, the incidence of AFF was calculated to be 278 per 100,000 person-years. Our single-center study found that bisphosphonates were commonly used long term by Japanese patients with SLE. As AFF is not rare, AFF should be cared in patients with SLE.

Keywords Systemic lupus erythematosus · Glucocorticoid-induced osteoporosis · Bisphosphonate · Guideline · Atypical femoral fracture

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that usually requires glucocorticoid therapy. Higher glucocorticoid doses serve as induction therapy and moderate-to-low doses are often used as long-term maintenance therapy. Thus, the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) is a particularly important issue; guidelines have been published by many medical societies and countries [1–5]. The prescription rates of anti-osteoporotic drugs for patients treated with glucocorticoids have been reported low [6–10]. In Japan, the guideline on the Management and Treatment of Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 Update (GIOP guideline) is widely used by medical practitioners for GIOP treatment [1]. When patients commence

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glucocorticoid therapy of ≥ 3 month duration, their risk factors must be scored. When the score is ≥ 3, appropriate treatment is recommended. The first-line treatment recommended by the guideline is bisphosphonates, which are commonly prescribed worldwide and have been most useful for the prevention and treatment of GIOP. However, long-term (≥5 years) use increases the relative risk of atypical femoral fracture (AFF) [11]. Also, glucocorticoid use and/or associated complications (i.e., connective tissue diseases) are risk factors for AFF [12]; we previously reported a higher incidence of localized femoral periosteal thickening of the lateral cortex (beaking, which precedes AFF) in patients with autoimmune diseases on bisphosphonates and glucocorticoids [13].

Here, we assessed the prescription rates of bisphosphonates in terms of the GIOP guideline in patients with SLE. The duration of such use and the prevalence of AFF were also evaluated.

Subjects and methods

Subjects

In total, 270 patients with SLE were enrolled, who had submitted written applications of intractable disease to Japanese Ministry of Health, Labour and Welfare in 2016. All patients were diagnosed with SLE using the 1997 classification criteria of the American College of Rheumatology [14] and were treated in the Division of Nephrology and Rheumatology of Niigata University Hospital. Their clinical and treatment status, age, sex, and systemic lupus erythematosus disease activity index (SLEDAI) score were obtained from clinical records and the forms they had submitted to the above-mentioned ministry in 2016. The study protocol was approved by the ethics committee of Niigata University, Japan (no. 2017-0307) on January 26, 2018, and we adhered strictly to all relevant tenets of the Declaration of Helsinki.

The GIOP guideline

The GIOP guideline of the Japanese Society for Bone and Mineral Research [1] was used. When patients commit to ≥ 3 months of oral glucocorticoid therapy, clinical risk factors are assessed and scored as follows: prior fragility fracture (no, 0; yes, 7), age (years; < 50, 0; ≥ 50 and < 65, 2; ≥ 65, 4), daily glucocorticoid dose (milligrams; < 5, 0; ≥ 5 and < 7.5, 1; ≥ 7.5, 4), and lumbar bone mineral density (BMD; %young adult mean; ≥ 80, 0; ≥ 70 and < 80, 2; < 70, 4) (Table 1). When the total score is ≥ 3, appropriate treatment is recommended.

Table 1 Scoring for risk factors according to the GIOP guidelines of the Japanese Society for Bone and Mineral Research [1]

Risk factors	Score
Prior fragility fractures	
No	0
Yes	7
Age (years)	
< 50	0
≥ 50 and < 65	2
≥ 65	4
PSL dose (mg/day)	
< 5	0
≥ 5 and < 7.5	1
≥ 7.5	4
Lumbar BMD (% YAM)	
≥ 80	0
≥ 70 and < 80	2
< 70	4

When patients commit to ≥ 3 months of oral glucocorticoid therapy, the clinical risk factors are assessed and scored. When the total score is ≥ 3, appropriate treatment is recommended

GIOP glucocorticoid-induced osteoporosis, *PSL* prednisolone, *BMD* bone mineral density, *YAM* young adult mean

Treatment in accordance with the GIOP guideline

The GIOP guideline recommends alendronate and risedronate as first-line treatments and teriparatide, ibandronate, alfacalcidol, and calcitriol as alternative treatments. In this study, treatment with bisphosphonates, teriparatide, denosumab, and/or active vitamin D was considered to be appropriate in terms of the guideline.

Definition of AFF

Atypical femoral fracture history was explored by medical record review. Atypical femoral fractures was defined based on the American Society for Bone and Mineral Research Task Force revised case definition of 2013 [15]. Complete AFF was associated with femoral displacement. Incomplete AFF was defined as the development of a fracture line running from the tip of a localized bone reaction evident on an X-ray, without displacement of the femur. Treatments and laboratory data at AFF onset were also obtained from clinical records.

Results

Characteristics of the study subjects

The characteristics of all study subjects are shown in Table 2. The mean patient age was 51.7 ± 14.3 years (range

20–92 years) and 90.4% were female. The mean disease duration was 18.9 ± 12.0 years. The mean SLEDAI score was 6.59 ± 4.80. Prednisolone (PSL) was prescribed for 257 (95.2%) patients at a mean dose of 10.0 ± 3.3 mg/day.

Table 2 Characteristics of the study subjects

	Mean ± SD	Min.–Max.
Age, years	51.7±14.3	20–92
Female, *n* (%)	227 (90.4)	
Age at disease onset, years	32.8±14.5	8–80
Disease duration, years	18.9±12.0	0.5–9.7
SLEDAI score	6.6±4.8	0–34
Prednisolone use, *n* (%)	257 (95.2)	
Prednisolone dose, mg/day	10.0±3.3	3–27
History of bisphosphonate use, *n* (%)	207 (76.7)	
Immunosuppressive drugs used		
Tacrolimus, *n* (%)	54 (21.5)	
Mizoribine, *n* (%)	25 (10.0)	
Azathioprine, *n* (%)	15 (6.0)	
Hydroxychloroquine, *n* (%)	14 (5.6)	
Cyclosporine, *n* (%)	8 (3.2)	
Mycophenolate mofetil, *n* (%)	6 (2.4)	
Methotrexate, *n* (%)	2 (0.8)	
Combinations of two or more agents, *n* (%)	24 (9.6)	

SLEDAI systemic lupus erythematosus disease activity index

GIOP guideline treatment

As a score ≥ 3 is required to trigger treatment under the GIOP guideline, we explored whether patients attained this score. First, the PSL dose was evaluated (Fig. 1). Of all patients, 205 (75.9%) took PSL at ≥ 7.5 mg/day (score 4) and 48 (17.8%) took PSL at ≥ 5 and < 7.5 mg/day (score 1). Among patients taking PSL at ≥ 5 and < 7.5 mg/day (score 1), 39 (14.4%) patients were aged ≥ 50 years (score ≥ 2); the total score afforded by the PSL dose, and age was thus ≥ 3. Of the remaining nine patients, three evidenced reduced lumbar BMD (total score ≥ 3), but three did not, and no prior fragility fracture was noted in their medical records (total score 0). The remaining three patients had not undergone BMD evaluation and were thus excluded. Four (1.5%) patients were on PSL doses of > 0 and < 5 mg/day (score 0), and all were aged ≥ 65 years (total score ≥ 4). Thirteen (4.8%) patients were not taking PSL. Thus, 251 (93.0%) patients had total scores ≥ 3 (Fig. 2).

Treatment with bisphosphonates in accordance with the GIOP guideline

Of patients whose scores were ≥ 3 ($n = 251$), treatment was in line with the GIOP guideline in 85.7% ($n = 215$; Table 3 and Fig. 2). Bisphosphonate was taken by 66.1% of patients (Table 3), and 76.7% (207/270) had histories of bisphosphonate usage (Table 2). Denosumab was used by 3.6% (9/251), anti-resorption drugs by 69.7% (175/251), and teriparatide by 1.2% (3/251) of patients (Table 3). Active vitamin D was used alone by 15.1% of patients

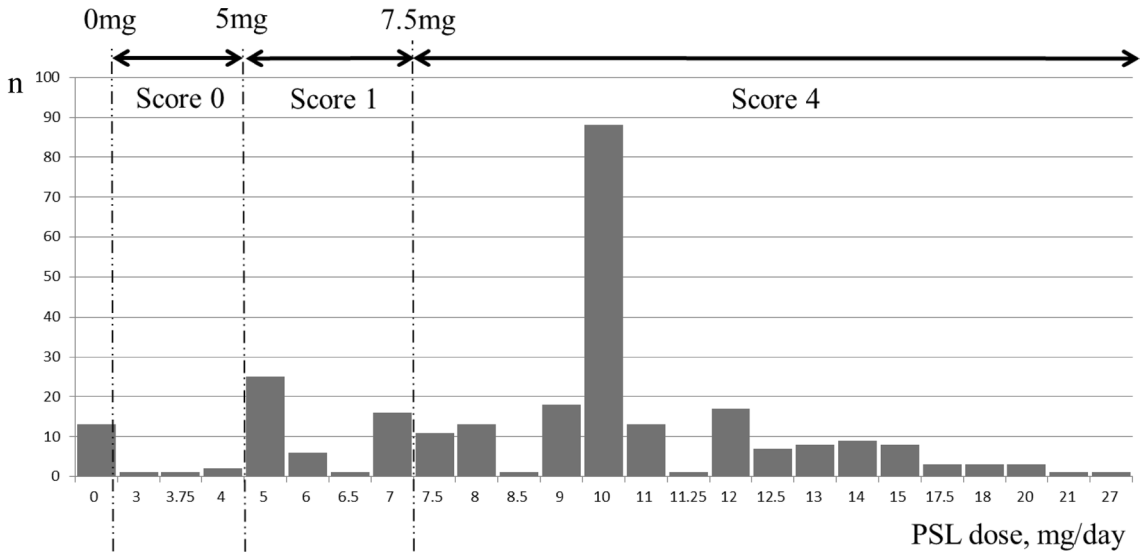

Fig. 1 Prednisolone doses and GIOP guideline scores. In total, 201 (75.9%) patients took PSL at doses ≥ 7.5 mg/day (score 4). Forty-eight (17.8%) took PSL at ≥ 5 but < 7.5 mg/day (score 1). Four (1.5%) took PSL at > 0 but < 5 mg/day (score 0). Thirteen (4.8%) patients did not take PSL

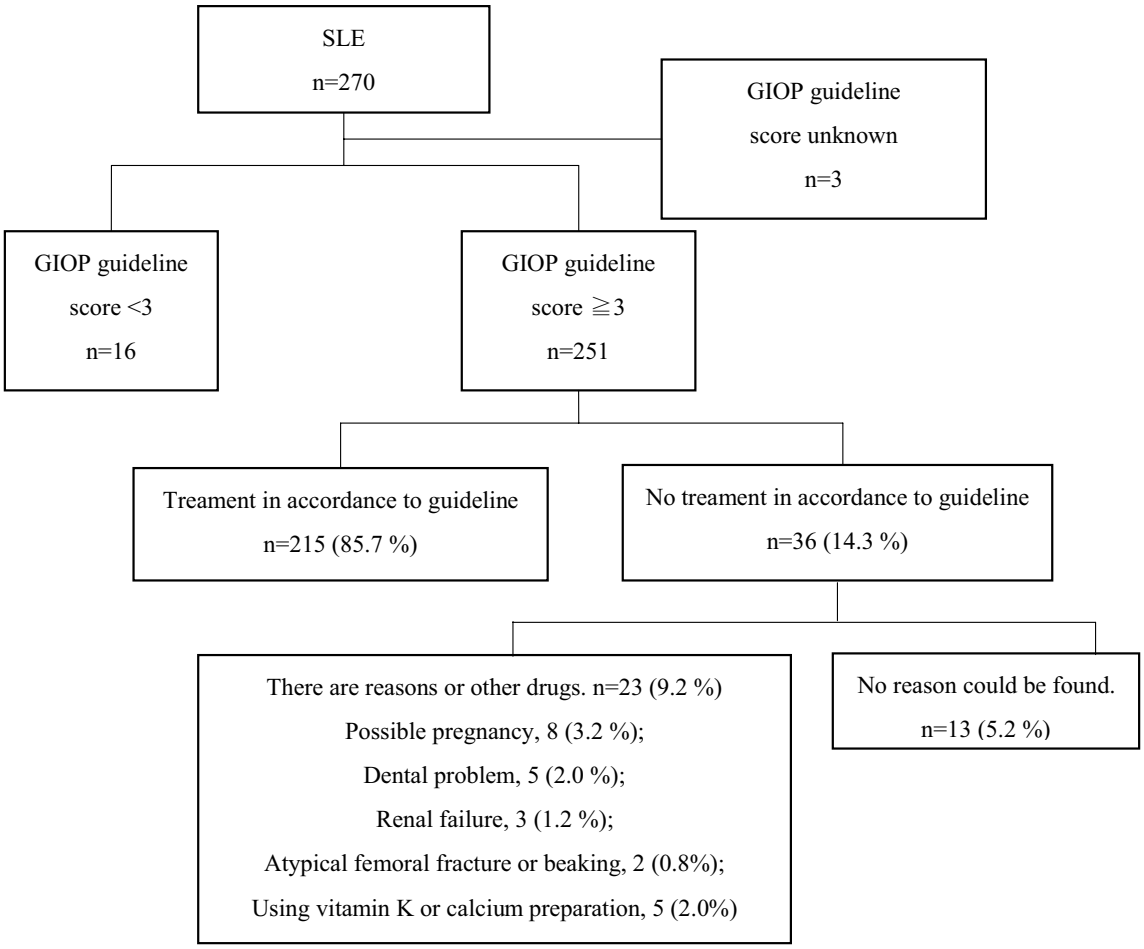

Fig. 2 Compliance with the GIOP guideline for patients with SLE. *SLE* systemic lupus erythematosus, *GIOP* glucocorticoid-induced osteoporosis

and in combination with anti-osteoporosis drugs by 30.7% of patients. Among patients not treated in accordance with the GIOP guideline ($n=36$, 14.3%), the medical records explained why 23 (9.2%) patients did not meet the guideline or took other anti-osteoporosis drugs. The reasons were possible pregnancy ($n=8$, 3.2%), dental problems ($n=5$, 2.0%), renal failure ($n=3$, 1.2%), and AFF or localized periosteal thickening of the lateral cortex (beaking) evident on femoral X-ray ($n=2$, 0.8%). Five patients were taking vitamin K or calcium preparations. No explanation for non-compliance was evident in the medical records of the remaining patients ($n=13$, 5.2%).

Duration of bisphosphonate use

Of patients taking bisphosphonate ($n=166$), 32 (19%) had taken the drug for <3 years, 26 (16%) for ≥ 3 and <5 years, 56 (34%) for ≥ 5 and <10 years, and 52 (31%) for ≥ 10 years (Fig. 3).

AFF prevalence

Five (1.9%) of 270 patients with SLE and 2.0% of patients with scores ≥ 3 (5/251) had histories of AFF (Table 4). Three patients had experienced complete AFF and had undergone open reduction and internal fixation (ORIF). The other two patients had experienced incomplete AFF and did not consent to ORIF. All five patients had taken moderate doses (≥ 10 mg/day) of glucocorticoids and were comparatively young (<60 years of age). Four had experienced AFF after using bisphosphonate for ≥ 3.5 years. For the patients who had taken bisphosphonates in the past, or who were currently on bisphosphonates, the prevalence of AFF was 1.9% (4/207) and the incidence of AFF were calculated as 278 per 100,000 person-years.

Table 3 Anti-osteoporosis drugs used

Anti-osteoporosis drug	n	(%)		
Bisphosphonate	166	(66.1)	n=175 (69.7%)	n=215 (85.7%)
Alendronate	98	(59.0)		
Minodronate	51	(30.7)		
Risedronate	14	(8.4)		
Ibandronate	1	(0.6)		
Etidronate	1	(0.6)		
Denosumab	9	(3.6)		
Teriparatide	3	(1.2)		
Active vitamin D	115	(45.8)		
Active vitamin D only	38	(15.1)		
Vitamin K	9	(3.6)		
Calcium preparations	48	(19.1)		
Combinations of two or more agents	77	(30.7)		

Of patients with scores ≥3 ($n=251$), 85.7% ($n=215$) were treated in compliance with the GIOP guideline. Bisphosphonates were used by 66.1% and denosumab by 3.6% of patients. Thus, anti-resorption drugs were taken by 69.7% of patients

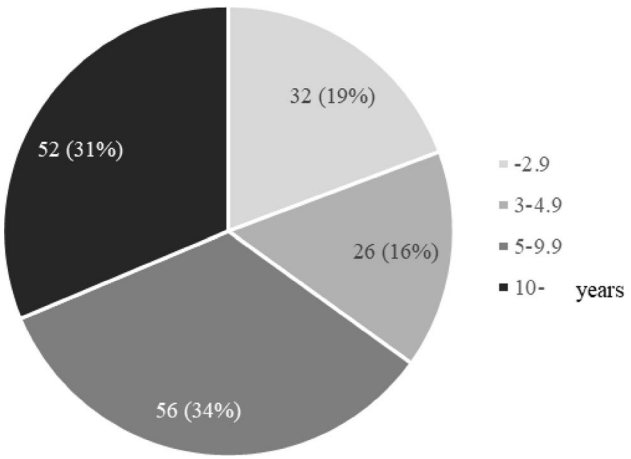

Fig. 3 Duration of bisphosphonate use. Of patients taking bisphosphonates ($n=166$, 66.1%), the durations of use were as follows: <3 years, 32 (19%); ≥3 but <5 years, 26 (16%); ≥5 but <10 years, 56 (34%); and ≥10 years, 52 (31%). The data are numbers with percentages

Discussion

Although low prescription rates of anti-osteoporosis drugs have been reported [6–10], we found that most patients with SLE were treated in line with the GIOP guideline in this study. The 2005–2010 National Health and Nutrition Examination Survey of the United States revealed that at least 50% of post-menopausal females and male patients aged ≥50 years needed anti-osteoporosis drugs in line with the 2010 American College of Rheumatology (ACR) recommendations for prevention and treatment of GIOP; however, the rate of self-reported anti-osteoporosis drug use was <30% [10]. In France, bisphosphonates were used by only 12% of patients on glucocorticoids, and calcium and/or vitamin D by 18%, as revealed by analysis of a public health insurance database [6]. In that cohort, the number of patients with SLE was small; most patients had rheumatoid arthritis (20%), autoimmune diseases including SLE (13%), chronic respiratory failure (13%), asthma (10%), and inflammatory bowel disease (8%). As SLE treatment usually commences with high-dose (≥7.5 mg/day) PSL, the Japanese GIOP guideline score is ≥4 at this time. Thus, rheumatologists usually combine PSL treatment with bisphosphonates. When patients require ≥7.5 mg PSL/day, bisphosphonates are prescribed long term, even when the patients are young and the lumbar BMD is high. This practice explains why patients with SLE are on long-term bisphosphonate treatment.

In general, AFF is rare; the absolute risk is very low compared with that of osteoporotic fracture; the incidences of

Table 4 Characteristics of patients at the time of atypical femoral fracture

Case	1	2	3	4	5
Age, years	53	36	49	59	54
Sex	Female	Female	Female	Female	Female
AFF	Complete	Complete	Complete	Incomplete	Incomplete
Right/left	Left	Bilateral	Left	Right	Right
Part region	Sub-trochanteric	Sub-trochanteric	Sub-trochanteric	Sub-trochanteric	Sub-trochanteric
Disease duration, years	5.5	7	5	26	15
Bisphosphonate use	–	ALN	ALN	ALN	ALN
Duration of bisphosphonate use, years	–	3.5	5.0	4.8	7.1
PSL dose, mg/day	15	14	10	12.5	10
Duration of PSL use, years	5.4	3.5	5.0	26	10
Active vitamin D use	–	–	–	+	–
Diabetes mellitus	–	–	–	–	+
Prodromal pain	–	–	+	+	+
Treatment	ORIF	ORIF + VD	ORIF + PTH	VD	PTH
Serum calcium adjusted by the albumin level, mg/dL	9.5	9.9	9.1	9.2	9.9
Serum phosphate, mg/dL	2.7	3.2	2.6	2.3	2.9
Serum alkaline phosphatase, U/L	244	236	184	161	326
Serum NTx, nmol BCE/L	19.8	10.2	9.8	20	11.8
Serum ucOC, ng/mL	N.D.	2.06	0.94	0.41	1.58

AFF atypical femoral fracture, *PSL* prednisolone, *ALN* alendronate, *ORIF* open reduction and internal fixation, *PTH* teriparatide, *VD* active vitamin D, *NTx* type I collagen cross-linked N-telopeptide, *ucOC* undercarboxylated osteocalcin, *N.D.* not determined

AFF were 16 and 113 per 100,000 person-years in those treated with bisphosphonates for 5 and 10 years, respectively [11]. However, the incidence in patients with SLE who had taken bisphosphonates in the past or who were currently on bisphosphonates was higher, i.e., 278 per 100,000 person-years. Apart from long-term bisphosphonate usage, glucocorticoid therapy posed a risk of AFF [12]. We previously reported a high prevalence (8–10%) of localized femoral periosteal thickening of the lateral cortex (beaking, which may precede AFF) in patients with autoimmune diseases, including SLE (56%), who were on both bisphosphonates and PSL [13]. One patient suffered a complete AFF at the beak within the 2-year observation period of the cited study. Together, the data suggest that long-term use of bisphosphonates combined with moderate PSL doses (as is often the case in patients with SLE) may create a risk of AFF.

AFF was first considered to reflect severely suppressed bone turnover (SSBT) [16]. Using bone histomorphometric analyses, we recently showed that SSBT was not always associated with AFF, and that bone formation was inhibited more severely in the sub-trochanteric than the diaphyseal AFF group and the higher glucocorticoid doses were prescribed in the former group [17]. All of our patients with AFFs exhibited the sub-trochanteric condition and were on moderate PSL doses (≥ 10 mg/day). Bisphosphonates inhibit the bone absorption associated with initiation of high-dose glucocorticoids, but chronic bisphosphonate use may induce SSBT. Glucocorticoids, which mainly inhibit bone formation, may also increase the risk of AFF. Indeed, one patient with AFF in the present study had never taken a bisphosphonate; rather, this patient was on a moderate PSL dose over many years. Low vitamin D levels have also been reported to increase the risk of AFF [18, 19]; only one of our five patients with AFFs was taking active vitamin D. Tapering of the PSL dose accompanied by the introduction of immunosuppressants and active vitamin D might reduce the incidence of AFF in patients with SLE. Moreover, regular femoral X-rays are essential to screen for the localized femoral reaction (beaking) that precedes AFF [13]. When beaking is evident, bisphosphonate discontinuation with a switch to vitamin D supplementation or teriparatide therapy might improve the prognosis or at least prevent exacerbation of the condition [20].

In the present study, 65% of patients with SLE had used bisphosphonates for ≥ 5 years, and the four patients with AFFs had taken such drugs for ≥ 3.5 years. Long-term (especially ≥ 5 years) bisphosphonate use is a risk factor for AFF; drug holidays have been considered for post-menopausal women with osteoporosis [11] treated with oral bisphosphonates for ≥ 5 years who exhibited no osteoporotic fracture and who had BMD T-scores > − 2.5. Furthermore, goal-directed osteoporosis treatment has been proposed in

primary osteoporosis; the goals are the absence of osteoporosis fracture, and an acceptable BMD and/or fracture risk assessment tool (FRAX) score [21]. Glucocorticoid-induced osteoporosis is not, of course, synonymous with post-menopausal osteoporosis; however, if the recommendations were to apply to patients with SLE, many young patients would be included in the drug-holiday group or would have achieved the goals.

Some other GIOP guidelines deal with the long-term use of bisphosphonates. The 2013 update of the UK National Osteoporosis Guideline Group recommended reconsideration of drug holidays in patients taking < 7.5 mg PSL/day [4, 5]. The French Society for Rheumatology and Osteoporosis Research and Information Group, in collaboration with four learned French societies, mentioned that appropriateness of long-term bisphosphonate therapy in patients receiving long-term glucocorticoid therapy should be considered as professional consensus [3]. The ACR GIOP guideline was updated in 2017 [2]. When a moderate-to-high fracture risk persists even after 5 years of bisphosphonate therapy, continuous use of oral bisphosphonate for 7–10 years was suggested, after consideration of the risks of AFF and jaw necrosis. More importantly, the updated ACR guideline contained separate recommendations for those aged > 40 and < 40 years; younger patients were to take less bisphosphonates even if they were on ≥ 7.5 mg PSL/day. Further prospective studies are needed to explore the safety and effectiveness of bisphosphonate drug holidays in terms of GIOP.

The major limitations of our study are that the work was a single-center retrospective study, the sample size was small, patient evaluation of short duration, and a control group was lacking. Systemic lupus erythematosus treatment strategies vary widely among hospitals and/or rheumatologists; our findings may not apply to all patients with SLE. Recently, more immunosuppressants for patients with SLE have been approved in Japan; reduction of the PSL dose is becoming easier, and the incidence of AFF may fall in the near future. Not all patients were screened AFF by X-rays; under-detection of subclinical AFF might be present.

In conclusion, most Japanese patients with SLE were treated in line with the GIOP recommendation; our single-center retrospective study found that bisphosphonates were frequently used. As patients with SLE may require low-to-moderate-dose PSL therapies in the long term, bisphosphonates are commonly prescribed long term, regardless of BMD or age. Also, our five patients with AFFs were taking moderate PSL doses (≥ 10 mg/day), and four had been taking bisphosphonates for ≥ 3.5 years. The incidence of AFF among patients with SLE who had taken bisphosphonates in the past or who were currently on bisphosphonates was high. AFF is not a rare complication and the development thereof needs to be monitored in patients with SLE.

Author contributions HS, NK, AW, DK, TN, and YW collected and analyzed the data. HS wrote the initial draft of the manuscript. NK, TK, YS, MN, EN, and IN assisted in the interpretation of the data and preparation of the manuscript. All of the authors have critically reviewed the manuscript and approved the final version of the manuscript.

Compliance with ethical standards

Conflicts of interest All authors have no conflicts of interest.

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